Mechanisms of therapeutic effects of rhubarb on gut origin sepsis

CHEN De-chang 陈德昌 and WANG Lü 王虑*

It is proposed that gut-liver-lung axis plays an important role in the pathophysiologic development of the critical illness, and it induces excessive inflammatory response *in vivo* and multiple organ dysfunction syndrome. The mechanisms of therapeutic effects of rhubarb on critical patients are studied based on the theory of Chinese traditional medicine. Researches demonstrate that rhubarb can be used to protect gut barrier, maintain intestinal microecological environment and prevent bacterial translocation. It also can be used to inhibit the release of inflammatory mediators by liver inflammatory-effector cells, reduce inflammatory reaction in the liver and protect hepatic cell functions. Furthermore, rhubarb can be used to reduce pulmonary vascular permeability and extenuate pulmonary edema, inhibit the release of neutrophil myeloperoxidase, and lower the level of inflammatory response and decrease inflammatory mediators in circulation. The above results indicate that rhubarb may interrupt or partly interrupt the gut-liver-lung axis after trauma and reduce the intensity of systemic inflammatory response syndrome. Therefore, rhubarb may obviously lower the incidence of multiple organ dysfunction syndrome and be used to prevent and treat systemic inflammatory response syndrome and multiple organ dysfunction syndrome after trauma.

Key words: ***Sepsis; Systemic inflammtory response syndrome; Medicine, Chinese traditional***

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Gastrointestinal tract is the internal organ that communicates with the outside. When injuries happen, the symptom of gastrointestinal tract is usually covered up by the clinical manifestation of original diseases. Studies show that the gastrointestinal mucosa barrier is easily damaged after trauma because of severe stress. Enterogenous bacteria and toxins could invade distant organs and circulation system *via* portal vein and alimentary duct, and be eliminated by the liver and lung which receive venous blood and lymph fluid from the gastrointestinal tract respectively. The inflammatory effector cells in the liver and lung may be activated by the enterogenous bacteria and toxins, release many cytokines and inflammatory mediators, and then induce systemic inflammatory reaction and gut origin sepsis. It is believed that the gut, liver and lung play a critical role in development of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). Therefore, enough attention should be paid to the pathophysiologic development of the critical illnesses. Nowadays, there is no ideal method to treat and prevent SIRS and MODS in Western medicine. However, many studies have revealed that rhubarb might have a good pharmacological effect on gut origin sepsis, and could interrupt the pathophysiologic process of SIRS and MODS. Here are some evidences about the mechanisms of rhubarb on SIRS.

Hypothesis about gut-liver-lung axis

Under the pathological condition of severe trauma, shock and infection, it is the common case that edema, erosion and ulcer develop in the gastrointestinal mucosa because of intense stress reaction. The barrier of intestinal mucosa is destructed and the bacteria and toxins from the intestinal tract will invade the liver *via* the portal vein. Thus, the gastrointestinal tract becomes an undrained abscess. The liver is the first physical barrier next to the gut. Kupffer's cells, the main effector cells in the liver, accounts for 70% of all phagocytes over the body, and their capacity of phagocytosis ac-

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Department of Emergency and Critical Care Medicine, Changzheng Hospital, Second Military Medical University, China (Chen DC and Wang L).

*Corresponding author: Tel: 86-21-81885843, E-mail: icudcchen@yahoo.com.cn

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counts for 95% of that over the body. Therefore, Kupffer's cells have a tremendous potential capability of inducing systemic inflammation reaction. As a result, Kupffer's cells have a two-side effect. On the one hand, Kupffer's cells can eliminate enterogenous bacteria and toxins. On the other hand, they will also be activated to release generous cytokines and inflammatory mediators leading to severe systemic inflammation reaction at the same time. Then, SIRS may be enhanced in the liver first. Hepatic vein blood, which contains generous cytokines and inflammatory mediators, return to the lung, accompanied with lymph fluid from gastrointestinal tract. Consequently, the macrophages in the lung tissue are activated and participate in systemic inflammatory reaction. Gut-originated septic reaction may be further aggravated by lung, and the inflammatory reaction in the lung feeds back to the gut and liver through blood circulation. In the end, a pathway of gut-liver-lung cascade reaction, also named gut-liver-lung axis, is finally formed. Systemic inflammatory reaction is amplified in this axis and the gastrointestinal mucosa injury may persistently exist because of vicious cycle of the inflammatory reaction formed in the gut-liver-lung axis. The bacteria and toxins from the intestinal tract constantly invade the liver, lung and blood circulation. Eventually, the uncontrolled SIRS may induce MODS.

Rhubarb is one kind of traditional Chinese herbs. According to an ancient Chinese medicine book Shennong's Herbal, it has three main pharmacological effects. The first one is to clean up the dyspeptic contents in gut and make intestinal tract unobstructed; the second one is to eliminate internal toxins and attenuate inflammatory reaction; the third one is to enhance metabolism and improve organ function. In our previous studies, critically ill patients suffered from gut origin sepsis were treated with rhubarb based on the above theory of Chinese traditional medicine. The pathway of gut-liver-lung cascade reaction was broken and SIRS became self-limited from the uncontrolled. Consequently, the pathophysiologic process of SIRS was inhibited and the development of MODS was prevented. Because of its pharmacological effect on gastrointestinal tract, rhubarb can be used to protect gut barrier, prevent bacterial translocation from the gut and promote gastrointestinal motility to relieve toxic enteroparalysis. Furthermore, rhubarb also can be used to inhibit activation of inflammatory effector cells and decrease the synthesis and release of inflammatory meditators in the gut-liver-lung axis. In addition, according to the theory of Chinese traditional medicine, in which it is believed that the lung is closely corresponding to the gut, rhubarb can be used to protect the lung by way of its pharmacological effects on the gut.

Mechanisms of therapeutic effects of rhubarb on gut origin sepsis

There are three stages of the pathophysiologic process in critical illness: acute stress reaction, sepsis and organ function recovery or multiple organ failure in turn. The overall therapeutic target is to relieve stress reaction, shorten the course of stress reaction, go directly into the stage of organ function recovery without sepsis, and prevent the development of MODS. Main puzzles in the stress reaction and sepsis stage are refractory shock, uncontrolled SIRS, pathologically supply-dependent oxygen consumption, capillary leakage, organ dysfunction, etc. Studies have revealed that the gut has a potential effect on the above pathophysiologic processes, and it is the critical organ for treatment. Clinical and animal studies have revealed that blood flow in gastrointestinal mucosa decreases, accompanied by the decline of gastric acid secretion and the derangement of neuroendocrine function in critical illness.[1-3] Furthermore, the application of H_2 receptor blocker and ion pump inhibitor in critical illness alkalifies intragastric environment, which is favorable to the growth and multiplication of the bacteria in the stomach. When the gut barrier is damaged, the bacteria and toxins delivered from the stomach may have an opportunity to translocate to distant organs and circulation system. Therefore, the pathophysiologic process caused by the original disease is aggravated. Currently, fewer methods can be used to control bacterial translocation.

According to the theory of Chinese traditional medicine and Western medicine, rhubard, a Chinese herb, has been used to treat gut failure. An animal study has demonstrated that the incidence of bacterial translocation from gut to liver, spleen and mesenteric lymph nodes are 75.0%, 75.0% and 93.8%, respectively at 24 hours after shock resuscitation in a hemorrhagic shock model. Moreover, the concentration of endotoxin in systemic venous blood increases to 341.7% of that before shock. After rhubarb treatment, the number of the bacteria translocation from gut to lung, spleen and mesenteric lymph nodes decreases to 2.1%, 3.8% and 9.1% of that in

shock group, and the level of endotoxin concentration in systemic venous blood also decreases by 39.6%.[4] Furthermore, it is observed that the epithelial cell layer of intestinal mucosa gets thicker and the goblet cells in intestinal mucosa greatly proliferates after rhubarb treatment.[5] In a burn injury model, the permeability of rat intestine mucosa increases, and the level of endotoxin, absorbed from intestinal tract, in portal venous blood is 2.2 times of that in systemic venous blood at 24 hours after burn injury. However, after rhubarb treatment in the burned rats, the concentration of endotoxin in portal venous blood obviously decreases by 51.3%, compared with that in burn plus endotoxin-hit group.[6] The therapeutic effects of rhubarb on gut is probably related with the following pharmacological mechanisms: Rhubarb can improve the blood perfusion of gastrointestinal mucosa. In a hemorrhagic shock model, the blood flow volume in gastric mucosa, small intestine mucosa and mesenterium is decreased to 42.2%, 46.4% and 46.1% of that in control group at 24 hours after shock resuscitation. Moreover, the hypoperfusion of gastrointestinal mucosa could not be corrected by sufficient volume resuscitation. Nevertheless, the blood flow volume in gastrointestinal mucosa and mesenterium is recovered to the level of control group after rhubarb treatment.[1] Rhubarb also has a protective effect on mitochondrial respiratory chain in intestinal mucosa. In a burn injury model, the integrality of mitochondrial respiratory chain in endothelial cells of intestinal mucosa is destructed by burn injury, whereas rhubarb could attenuate the loss of cytochrome aa3, b, c and c1, increase respiratory exchange ratio of the mitochondria, and diminish leakage of oxygen free radicals from the mitochondria in hypoxia status.[7-9] At last, rhubarb potentially inhibits expression of the gene of tumor necrosis factor receptors 1 and 2 in the endothelial cells of intestinal mucosa.[10]

Clinical study has revealed that haemostasis is effective in 71.2% of patients with stress ulcer accompanied by gastrointestinal bleeding and gut peristalsis is recovered in 76.1% of the patients with toxic enteroparalysis in critical illness after rhubarb treatment. Furthermore, rhubarb could improve the tolerance of enteral feeding in 52.2% of patients with gut failure.[11] The study also shows that rhubarb has a preventive effect on stress ulcer with gastrointestinal bleeding and toxic enteroparalysis. The incidence of gastrointestinal bleeding and toxic enteroparalysis decreases to 14.8% and 11.0% from 18.8% and 22.1% in control group respectively after rhubarb treatment. In addition, the intramural pH value (pHi), an indicator of blood perfusion in gastrointestinal mucosa, is extremely low in critical illness. However, after rhubarb treatment, the pHi in gastric and rectal mucosa approaches to that in control group.[11]

The pathological basis of gut origin sepsis is the destruction of gastrointestinal mucosa barrier. In critically ill patients, the lesion, long existing in gastrointestinal mucosa, may cause continuous invasion of the bacteria and toxins from gastrointestinal tract to circulation system, and then induce persistent activation of the monocyte-macrophage system. A number of cytokines and inflammatory mediators, released by monocytes and macrophages, can make SIRS uncontrolled and subsequently induce MODS. Because of the above pharmacological mechanisms, rhubarb may interrupt the first link of gut-liver-lung axis and remove the pathological basis of SIRS and MODS.

Effect of rhubarb on inflammatory reaction in the liver

Liver, the first physical barrier next to the gut, filters the venous blood from gastrointestinal tract. After severe trauma, the intestinal mucosa barrier can be destructed by severe stress, and then enterogenous bacteria and toxins invade the liver, activate Kupffer's cells. On the one hand, the activated Kupffer's cell in liver can eliminate the enterogenous bacteria and toxins;on the other hand, it can release a large number of cytokines and inflammatory mediators such as TNF-α and IL-1, and aggravate SIRS. In a burn injury model, studies show that burn plus endotoxin hit could induce the gene expression of TNF-α and IL-1β in the liver. Moreover, the concentration of TNF-α in liver tissue is also higher at two orders of magnitude than that in serum. Whereas, rhubarb could evidently inhibit the gene expression of TNF-α. The extent of the inhibition of TNF-α is as high as 73.9% of that in burn plus endotoxin-hit group. The concentration of TNF-α in the hepatic tissue is decreased by 65.4% compared with that in burn plus endotoxin-hit group after rhubarb treatment. Rhubarb almost completely suppresses the gene expression of IL-1β.[6] The gene expression of tumor necrosis factor receptor ($TNFR_1$ and $TNFR_2$) in hepatic cells induced by burn injury plus the second hit by endotoxin is significantly inhibited because of rhubarb treatment.[12]

Moreover, rhubarb is also a scavenger of oxygen free radicals. The activity of glutathione peroxides and peroxide dismutase in hepatic tissue after rhubarb treatment is increased by 288.0% and 28.1% of that in burn group respectively. The activity of xanthine oxidase is decreased by 60.5% of that in burn group.[13] Further studies have revealed that rhubarb has a protective effect on the mitochondrial respiratory chain of hepatic cells. Rhubarb could attenuate the loss of elements of mitochondrial respiratory chain, increase the energy charge and decrease the leakage of oxyradicals from the mitochondria in hepatic cells.[14]

The above studies demonstrate that rhubarb could inhibit inflammatory reaction in the liver under pathological conditions such as trauma and sepsis, which means that the inflammatory response is attenuated in the second link of gut-liver-lung axis. Liver is a huge chemical plant in human body. It has important functions such as energy metabolism, detoxication and secretion, etc. In critically ill patients, the hepatic functions can be injured by enterogenous bacteria, toxins and inflammatory cytokines because of gastrointestinal dysfunction. Therefore, the application of parenteral and enteral nutrition is limited. The host defense may be impaired by malnutrition. At last, sepsis will be aggravated and a vicious cycle is developed: toxic enteroparalysis, hepatic dysfunction, energy metabolism disorder, host defense hypofunction, and sepsis aggravation. This is a very severe clinical condition and can lead to poor prognosis. Rhubarb can relieve toxic enteroparalysis, inhibit the inflammatory reaction in the liver, protect hepatic function and prevent development of the above vicious cycle, which is beneficial for the treatment and rehabilitation of critically ill patients after trauma.

Effects of rhubarb on intrapulmonary inflammatory reaction

The lung filters blood from the gastrointestinal tract and other tissues over the body. The functional condition of lung reflects the strength of systemic inflammatory reaction. Nevertheless, the inflammatory effector cells in the lung can deteriorate SIRS. In a model of gut ischemia-reperfusion, studies show that the permeability of pulmonary capillary to albumin increases to 415.8% and 400.0% of that in control group at 2 and 6 hours after gut reperfusion respectively; however, after rhubarb treatment, the permeability of pulmonary capillary to albumin decreases to 140.6% and 129.1% of that in control group respectively. The activity of myeloperoxidase (MPO) in the lung tissues increases to 260.6% and 274.8% of that in control group at 2 and 6 hours after gut reperfusion respectively, and after rhubarb treatment, it decreases to 92.4% and 103.2% of that in control group. The concentration of nitrogen monoxidum (NO) in the lung tissues increases to 903.6% and 1020.5% of that in control group at 2 and 6 hours after gut reperfusion respectively, and after rhubarb treatment, it decreases to 270.5% and 322.5% of that in control group. The activity of phospholipase A_2 (PLA_2) in the lung tissues increases to 235.5% and 244.4% of that in control group at 2 and 6 hours after gut reperfusion respectively, and after rhubarb treatment, it decreases to 101.8% and 104.6% of that in control group. In the same model, at 30, 60, 120 minutes after gut reperfusion, the level of TNF in the lung tissues increases to 6941.6%, 642.1%, and 342.1% of that in control group respectively, and after rhubarb treatment, it decreases to 584.3%, 348.1%, and 259.6% of that in control group respectively.[15]

The above results show that there is an internal connection between intestinal tract and lung, and it is consistent with the theory of Chinese traditional medicine — the lung is closely corresponding to the gut. The more severe the translocation of bacteria and toxins from gastrointestinal tract is, the more intense the intrahepatic inflammatory reaction will be. Therefore, the concentration of inflammatory mediators in pulmonary blood draining from the liver becomes higher and intrapulmonary inflammatory reaction becomes more intense. Consequently, the magnifying effects of the liver and lung on SIRS become more severe. Rhubarb has a manifestly intrapulmonary inflammatory reaction. Lung is the third link of gut-liver-lung axis. Therefore, rhubarb can prevent the magnification of inflammatory reaction by gut-liver-lung axis after trauma. At present, the mortality of ARDS induced by trauma and sepsis is still high. In Western medicine, there is no ideal remedy to improve the prognosis of ARDS except mechanical ventilation. Rhubarb can inhibit intrapulmonary inflammatory reaction and attenuate acute lung injury caused by excessive SIRS. Consequently, oxygen supply is increased and tissue oxygenation is improved, which can preserve organ function and shorten the period of mechanical ventilation in critically ill patients.

Effect of rhubarb on inflammatory reaction in circulation

Severe systemic inflammatory reaction is partially due to the involvement of gut-liver-lung axis in the pathophysiologic process of critical illness. Studies show that rhubarb could evidently inhibit the gene expression of TNF-α in blood monocytes, decrease the concentration of TNF-α, IL-6, and weaken the activity of platelet activating factor (PAF) and PLA_2 in blood.[16-18] Clinical researches demonstrate that in patients with MODS involving more than four organs, the survival rate of patients with rhubarb treatment is significantly higher than that of patients without rhubarb treatment.[19] SIRS is the pathophysiologic basis of MODS. In recent 10 years, a large number of resources are spent on the researches of SIRS and MODS all over the world. However, it remains a difficult issue in critical care medicine and no ideal method to prevent and treat the disease. The above results, about the effects of rhubarb on the inflammatory reaction in the liver, lung, and circulation, indicate that rhubarb may interrupt or partly interrupt the gut-liver-lung axis after trauma and reduce the intensity of SIRS. Therefore, rhubarb may obviously lower the incidence of MODS and be used to prevent and treat SIRS and MODS after trauma.

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